Pancreatic Cancer and Radiation Therapy

- **Why?**
  - *Is there a role for local therapy with radiation in a disease with such a high rate of distant metastases?*

- **When?**
  - *Resectable Disease*
    - Is there a role for post-op RT?
  - *Borderline Resectable Disease*
    - Does RT improve the rate of Ro resections?
  - *Locally Advanced Unresectable Disease*
    - Is there a benefit over chemotherapy alone?

- **How?**
  - *Technological Advances*
    - Stereotactic Body Radiation Therapy (SBRT)
    - Improved outcomes through dose escalation?
Resectable Pancreatic Cancer: Is there a role for post-op RT?

- Only 15% of patients have resectable disease at diagnosis
- Post-op chemo is standard of care
- Is there a role for post-op RT?

- GITSG 9173
- 42 pts randomized to observation or CRT after R0 resection
- **Survival benefit with CRT compared to surgery alone**
  - MS: 20 vs. 11 mths
  - 5 yr OS: 19 vs. 5%
- But treatment fields, prescription, and chemo are now outdated

Kalser et. al. Arch Surg 1985
Resectable Pancreatic Cancer: Is CRT superior to chemo alone?

- **ESPAC-1**
  - Only randomized trial comparing adjuvant chemo to CRT

- **Survival Worse w/CRT vs. No CRT:**
  - 5 yr OS 10% vs. 20%
  - MS 15.9 mths vs. 17.9 mths

- **Survival Improved w/Chemo vs. No Chemo:**
  - 5 yr OS 21% vs. 8%
  - MS 20.1 mths vs. 15.5 mths

- **But methodology flawed**
- **Is CRT really detrimental?**

Neoptolemos et. al. NEJM 2004
Data Using Modern RT Techniques: National Cancer Database (NCDB) Analysis

- Analysis of over 6000 patients with resected pancreatic adenocarcinoma identified in the NCDB
- 38% received adjuvant chemo; 62% received adjuvant CRT
- CRT was associated with improved survival on MVA and with propensity score matching

Rutter et al. Cancer 2015
Is there a Role for Adjuvant CRT with Modern Systemic Therapy and RT: RTOG 0848

**FIRST STEP:**
ADJUVANT SYSTEMIC TREATMENT

- **Arm 1:**
  - Gemcitabine alone or combination chemotherapy x 5 months

- **Arm 2:**
  - Gemcitabine + Erlotinib x 5 cycles (Arm 2 closed to accrual effective 4/02/14)

Evaluate To Confirm No Progression

**SECOND STEP:**
RT RANDOMIZATION
For Non-Progressing Patients

- **Arm 3:**
  - 1 month of gemcitabine or combination chemotherapy

- **Arm 4:**
  - 1 month of gemcitabine or combination chemotherapy followed by XRT with either capecitabine or 5-FU
Post-Operative Treatment Volume

- 45% (90 of 202) patients at JHU developed local recurrence after resection
- Sites of recurrences were mapped and 90% of recurrences were within close proximity of the celiac and SMA

- Standard fields encompass the tumor bed and regional nodes, but the area at risk for recurrence is likely smaller
- Reduced target volume:
  - Minimize toxicity
  - Could improve efficacy by allowing for dose escalation

Dholakia et al. IJROBP 2013
Conclusions: Resectable Disease

- Adjuvant chemo improves OS and is standard of care
- RTOG 0848 is evaluating the role of CRT in the context of modern chemotherapy and RT
  - Will there be a benefit as systemic therapies improve?
- Smaller treatment volume may reduce toxicities and allow for dose escalation, which may lead to improved local control
- Should we consider neoadjuvant therapy?
  - Current studies are evaluating whether chemo and/or RT in the neoadjuvant setting can improve control of micrometastatic disease and R0 resection rates
Borderline Resectable Disease

• Potential for resection with positive margins is increased due to proximity of the tumor to vasculature
  – Contact with the common hepatic artery
  – <180 degrees of contact with the SMA
  – >180 degrees of contact with the SMV or PV, or contour irregularity or thrombosis of the vein

• Survival after an R1 or R2 resection is comparable to survival in patients with unresectable disease

• Does neoadjuvant therapy improve outcomes?
  – Downstage tumor to improve R0 resection rate
  – Address micrometastatic disease
Borderline Resectable Disease: MDACC Experience

- 160 patients with BRPC
- 78% received pre-op gemcitabine-based chemo -> CRT
- 41% of patients underwent resection after neoadjuvant therapy
- 94% rate of R0 resections
- MS 40 mths with resection vs. 13 mths without surgery

Borderline Resectable Disease: Alliance A021101 Trial

- Prospective multicenter single arm study including 22 patients
- **Neoadjuvant mFOLFIRINOX x4 -> CRT**
  - 50.4 Gy with capecitabine
- 15 patients (68%) underwent resection
- Negative margins in 14
- <5% residual tumor in 5 patients
- pCR in 2 patients
- Median OS 21.7 mths
- 64% grade 3 or higher toxicity

- **Alliance A021501**
  - Neoadjuvant chemo + or - RT
  - Currently accruing

Katz et. al. JAMA Surg 2016
Locally Advanced Unresectable Disease

- 30-40% of patients have locally advanced unresectable disease at diagnosis
- Studies to date evaluating the addition of CRT to chemo have conflicting results

- ECOG E4201: CRT vs. Gemcitabine
- OS benefit w/CRT: MS 9.2 → 11 mths

- Induction Chemo → CRT vs. Chemo
- GERCOR retrospective
- After upfront chemo, improved OS w/CRT vs continued chemo: MS 11.7 → 15 mths
Locally Advanced Unresectable: LAP07 Trial

Induction Chemotherapy

- Gemcitabine
- Gemcitabine + Erlotinib

No Disease Progression

- Gemcitabine +/- Erlotinib
- Chemoradiation 54 Gy + Capecitabine +/- Erlotinib

Hammel et. al. JAMA 2016
Locally Advanced Unresectable: LAP07 Trial

- No OS benefit to CRT after 4 months of induction gemcitabine
  - MS 16.5 mths (chemo) vs. 15.2 mths (CRT)

- Significant local control benefit with CRT vs. chemo
  - Locoregional progression: 32% vs. 46%

- Prolonged treatment-free interval after CRT
  - 6.1 vs. 3.7 months

Hammel et al. JAMA 2016
Locally Advanced Unresectable

- CRT is still commonly employed in those patients without progression after maximal response or tolerance of upfront chemotherapy, for several reasons:
  - CRT results in a local control benefit and local progression can cause significant morbidity
  - The prolonged treatment-free interval is beneficial for patients with limited lifespan
  - Significant advances in systemic therapy have improved outcomes for LAPC and likely impact the role of radiation
Locally Advanced Unresectable: CRT with Modern Systemic Therapy

- In metastatic patients, survival is significantly improved with FOLFIRINOX and gemcitabine / nab-paclitaxel compared to gemcitabine alone.
- These regimens are increasingly used to treat locally advanced disease.
- Meta-analysis of first line FOLFIRINOX for LAPC:
  - Median OS = 24.2 months.
- Yale phase II study of mFOLFIRINOX for LAPC:
  - Median OS = 26.6 mths.
- With improved control of micrometastatic disease and distant progression, the addition of RT is more likely to be of benefit.

Stein et. al. BJC 2016
Locally Advanced Unresectable: Radiation Dose Escalation

• Technological Advances
  – Intensity Modulated Radiation Therapy (IMRT)
  – Stereotactic Radiation Therapy (SBRT)
    • Reduces treatment related toxicities
    • Allows for escalation of dose delivered
Intensity Modulated Radiation Therapy (IMRT)

- Radiation is delivered with multiple beams or arcs
- Beam intensity is varied across the treatment field
- Radiation dose better conforms to tumor target

**3D Conformal RT**

**IMRT**

- IMRT reduces ≥grade 2 GI toxicities compared to 3D-CRT for LAPC
- By limiting dose to neighboring normal tissues, IMRT allows for safe dose escalation to the tumor
Stereotactic Body Radiation Therapy (SBRT)

- Ablative dose of RT in 5 or fewer fractions
- Focally targeted to tumor volume with **minimal margin** (2-3 mm) and sharp dose fall-off gradients to avoid normal tissue
Respiratory Motion Management

- In order to reduce margins of treatment volumes, motion of tumor with respiration must be accounted for
  - 4-Dimensional planning CT to depict tumor motion
  - Respiratory gating to treat only in certain phases of respiratory cycle or
  - Abdominal compression to decrease tumor motion
Image Guidance

- Fiducial markers are placed in the tumor under EUS guidance
- CBCT obtained on the treatment machine prior to each fraction and merged with the planning CT
- Fiducials are used to align the pancreas
Locally Advanced Unresectable: Dose Escalation with Stereotactic Radiation

- Multi-institutional Prospective Trial (JHU, Stanford MSKCC)
  - 49 patients with unresectable pancreatic cancer
  - Gemcitabine x3 -> SBRT to 33 Gy (5 fractions of 6.6 Gy)
  - Median survival: 13.9 months
  - Local Control at 1 yr: 78%
  - Low rates of grade ≥2 toxicities (2% acute, 11% late)

Timmerman et. al., JCO 2014
Herman et. al., Cancer 2015
SBRT: Advantages

- Studies have not compared SBRT to conventionally fractionated CRT
- Potential advantages include:
  - Potential for enhanced biologic effect of larger fraction sizes and improved local response.
    - Local control of ~80% at 1 year compares favorably to historical controls, including the LAP07 trial (LC after CRT was 68%)
  - Shorter treatment time
    - Less time off of multi-agent chemotherapy
    - Less delay to surgery
    - Better tolerated
  - Immunomodulatory effect?
- Over 50 clinical trials currently evaluating SBRT in the management of pancreatic cancer
  - Phase III study of FOLFIRINOX + or − SBRT for LAPC
SBRT: Future Advances

- **Calypso Soft Tissue Beacon Transponders**
  - Electromagnetic transponders
  - Implanted in the tumor (17 gauge)
  - Target motion can be continuously tracked during treatment
  - Treatment is paused if the target moves out of tolerance
SBRT: Future Advances

• Dose escalation is limited by tolerance of neighboring bowel
  – Lung SBRT: BED ≥100 Gy delivered
  – Pancreas SBRT: BED ~55 Gy delivered

A Novel Absorbable Radiopaque Hydrogel Spacer to Separate the Head of the Pancreas and Duodenum in Radiation Therapy for Pancreatic Cancer

Rao et. al., IJROBP 2017
SBRT: Future Advances

- Human cadaver study
- Absorbable radiopaque hydrogel injected between the duodenum and pancreatic head under EUS guidance
- ~1cm of space achieved
- SBRT plans modeled on pre and post-hydrogel CT scans. Spacer resulted in significant reduction in dose to duodenum

Rao et. al., IJROBP 2017
SBRT and Immunotherapy

- Radiation upregulates PD-L1 expression in PDAC cell lines
- In mouse models:
  - RT -> tumor growth delay
  - Anti-PD-L1: no effect on tumor growth
  - Anti-PD-L1 and RT: synergistic effect with enhanced tumor response

Azad et. al., EMBO Mol Med 2017
Institutional Phase II Study for BRPC: Pre-operative mFOLFIRINOX and SBRT

Borderline Resectable Pancreatic Adenocarcinoma

EUS:
- Core Biopsies Banked
- Elastography

FOLFIRINOX x8 cycles

EUS:
- Fiducial Placement for SBRT
- Core Biopsies Banked
- Elastography

Stereotactic Body RT in 5 fractions

Surgical Resection
- Tissue Banked

FOLFIRINOX x4 cycles
Correlative Studies

- Evaluate the immunomodulatory effect of FOLFIRINOX and stereotactic radiation on the tumor and tumor microenvironment, and the prognostic and predictive value of immune markers
  - In collaboration with Kurt Schalper, MD, PhD and Marie Robert, MD
    - Pathology

- Evaluate EUS elastography measurements of tissue stiffness as a novel predictive and prognostic marker
  - In collaboration with James Farrell, MD and Harry Aslanian, MD
    - Gastroenterology; Interventional Endoscopy

- Evaluate circulating tumor DNA as a predictive and prognostic marker
  - In collaboration with Abhijit Patel, MD, PhD
    - Therapeutic Radiology
Conclusions

• In resectable disease, adjuvant chemo is standard but RTOG 0848 is evaluating the role of chemoradiation with modern systemic therapy
• In borderline resectable disease, neoadjuvant RT or SBRT may improve resectability
• In locally advanced disease, RT provides local control if disease does not progress after initial chemotherapy, and outcomes may improve with dose escalation techniques including SBRT
• There may be a new role for RT in combination with immune therapy